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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/580,561	05/26/2006	Fengqi Ye	SHA 140NP	5972

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EXAMINER	
BERCH, MARK L	

ART UNIT	PAPER NUMBER
1624	

MAIL DATE	DELIVERY MODE
09/08/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/580,561	YE ET AL.	
	Examiner	Art Unit	
	Mark L. Berch	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 August 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *24* is/are allowed.

6)☒ Claim(s) *16-23 and 25-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 08/05/2009 has been entered.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 16-23, 25-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Baltzer or English, these in view of Xiong(2004).

Baltzer teaches the concept of a mutual prodrug of β-lactam antibiotics and β-lactamase inhibitors; see title. These were formed in the exact same way applicants do, by esterifying both the β-lactam antibiotic and β-lactamase inhibitor to the same methylene group. The advantage of doing this over the alternative, a mixture of the two compounds, is set forth in the paragraph bridging pages 1183-1184, viz., that "both the antibiotic and the inhibitor are present simultaneously in appropriate balance at the site of the infection. This will not usually be the case when the two compounds are given as a combination ....

because each drug in a combination will have its own individual profile with respect to rate of absorption, distribution and duration of action." This established that one of ordinary skill in the art would be well motivated to prepare the mutual prodrug rather than the combination of β-lactam antibiotic and β-lactamase inhibitor, because the advantage to doing this is taught.

English has a very similar teaching. Again, sulbactam is linked in the same way to a penicillin. Page 346 notes the advantage to be expected: "There are several advantages inherent to carboxyl-terminated double-ester prodrugs for oral delivery of pharmaceutical agents. The carboxyl moiety imparts improved water solubility, especially as the pH rises, as in transit from the stomach to the small intestine. It also provides improved prospects for isolation of crystalline solids as free acids or as sodium salts, thus creating options to improve formulation of oral delivery forms. Another advantage is the formation of potentially innocuous organic diacids as by products after hydrolysis to the parent drug in vivo. Clinically, these advantages can be translated to drugs that are more efficacious, safe, and convenient to use. In summary, the acid-termination concept of ester prodrug design has provided novel and effective delivery forms for the β-lactamase inhibitor sulbactam. Similar application to other drugs in order to improve oral bioavailability, formulation, water solubility, and simultaneous byproduct formation is suggested." The "Similar application to other drugs" would render such an approach obvious to any other drug which was already known to be synergistic with sulbactam.

The two examples of the primary reference, compounds 3 and 4, both employ sulbactam as the β-lactamase inhibitor. The β-lactam antibiotic in both cases is a penicillin. However, it would be obvious to use any "β-lactam antibiotic", as that is what the reference

Baltzer teaches; again, see title and above cited paragraph. Likewise, English teaches "other drugs".

In Xiong (2004), note Table 2, which shows strong synergism between sulbactam and Cephalothin, Cefuroxime, Cefpodoxime, Cefotaxime, Ceftazidime and Ceftriaxone. Note that cefuroxime is the second species in claim 16. Therefore, it would be obvious to prepare the ester of sulbactam with any of these antibiotics to gain the advantages which the primary references teach is obtained by using the ester rather than the mixture of two drugs.

Some claims specify salts. This is not a patentable distinction, as β-lactams are routinely administered as salts, especially hydrochloride salts. Cefotiam hexetil hydrochloride, Cefcapene pivoxil hydrochloride, Cefalexin hydrochloride, Cefepime hydrochloride, and Cefozopran hydrochloride are some examples of this.

The earlier traverse was unpersuasive.

A. Applicants pointed to the age of the references (1980, 1989), and infers from this that "these compounds are difficult to obtain." The age of a reference, or that a given improvement appears after a long time lapse does not of itself prove that such change was unobvious. See ***In re Lechene***, 125 USPQ 396; ***In re McCarn***, 101 USPQ 411. The age says nothing about difficulty, and moreover, difficulty does not mean unobviousness.

B. Applicants next argued that "The present invention solves a technical problem which was desired to be solved for a long time but which had not be solved successfully." This is simply not true. Baltzer and English both made the mutual prodrug of β-lactam antibiotics and β-lactamase inhibitors, and sulbactam in particular, and both formed them in the exact same way applicants do, by esterifying both the β-lactam antibiotic and β-

lactamase inhibitor to the same methylene group. The only reason that these references don't anticipate is that neither used the exact permutation of β-lactam antibiotic and β-lactamase inhibitor. The solution of finding something better than a simple mixture of β-lactam antibiotic and β-lactamase inhibitor was already known. Thus, while applicants state that they "surprisingly successfully obtained...." their product, there is no reason to see any of this as a surprise.

C. Applicants next pointed to the selection of "specific performance and reaction conditions". It's not at all clear what specifically applicants refer to, but even if true, that would only be relevant to method of manufacture claims. If applicants are saying that the sulbactam esters cannot be made except for methods which applicants invented, then such an argument could overcome the rejection. However, applicants are not actually saying that, and its unclear how applicants could make such an argument, given that e.g. English certain seems to say that they can make the sulbactam esters.

D. Applicants state that their compounds have "an unexpected antibacterial effect". On what basis could the antibacterial effect possibly be considered unexpected?

E. Applicants argues "YR-1 and YR-2 have antibacterial activity in vitro which is nearly equal to that of the combination of parent drugs, and, for some bacterial strains, such as Proteus mirabilis, Bacillus preteus, Proteus morganii and Shigella flexneri, the antibacterial activities of YR-1 and YR-2 are veen better than that of the combination of parent drugs. Applicant respectfully submits that the above effects would not be obvious to one of ordinary skill in the art." This is unpersuasive for several reasons:

a. The testing is only done on derivatives of cefetamet and cefuroxime.

b. It is correct that in those 4 cases, the ester is better than the combination, for one or for both of cefetamet and cefuroxime. But in other cases, e.g. Pseudomonas aeruginosa 10124, Bacillus pneumoniae 46101, Bacillus aerogenes 45102, Citrobacter 48017, the results were the same. In some cases, one was the same, but for the other, the ester was actually worse, e.g. Candida eiferii 41002, Shigella sonnet 51081, Shigella bogdii 51313, and Diplococeus lanceolatus 31002. And in some cases, both were actually worse i.e. Staphylococcus aureus 26003, Salmonella enteritidis 50041, Salmonella typhi 50097, and E. coil 44102. This is perfectly normal (hence, not unexpected) --- some better, some the same, and some worse. In fact, taken as a whole, the ester was better than the combination in 6 cases, the same in 14, and worse in 12. That is more negative than positive.

c. Further, even in the cases where the ester is better, why is that unexpected? Both primary references teach that one expects the ester to be better than the physical combination.

In the response of 08/05/2009, applicants argue that the examiner's position "is based on a mistaken concept", although applicants do not state what that mistaken concept is, let alone why applicants believe that it is mistaken.

Applicants next argue that there are many ß-lactams and cite exhibit 1 (if applicants wish the Wikipedia references made of record, they must present a proper 1449, with the URL and date downloaded from the internet). The examiner agrees that the ß-lactams are "the most widely-used group of antibiotics". The examiner understands what the structures of penicillin and cephalosporin are.

Applicants next state, "Applicants wonder how the inventive step regarding a specific kind of the most widely-used group of antibiotics' be taken away by mere mention

in the Title of Baltzer of, "mutual pro- drug of β-lactam antibiotics and β-lactamase inhibitors" The examiner has not said that the title alone anticipates or renders obvious applicants entire invention. What the examiner has said is that the title conveys the "concept of a mutual prodrug of β-lactam antibiotics and β-lactamase inhibitors". As for the specific kind, that the examiner looks elsewhere to. The structure of esterifying both the β-lactam and the β-lactamase inhibitor to the same methylene group (called "the mutual prodrug" (Baltzer) or "carboxyl-terminated double-ester prodrugs"(English)), and the use of sulbactam as the β-lactamase inhibitor, is exactly what the primary references do. The specific cephalosporin is taught by the primary reference.

Applicants additionally wonder how there can be any expectation of an advantage, as the Examiner's considers is found in English on page 346, "There are several advantages inherent to carboxyl-terminated double-ester prodrugs for oral delivery of pharmaceutical agents. The carboxyl moiety imparts improved...." The expectation of advantage is what the reference teaches. The text's ""There are several advantages....." sets forth the advantage of the carboxyl-terminated double-ester prodrugs.

Next, applicants state, "Applicants believe that it is not well founded for the Examiner to have concluded merely by the "Similar application to other drugs", as the Examiner stated, "would render such an approach obvious to any other drug which was already known to be synergistic with sulbactam"." Why not? When the reference teaches "Similar application to other drugs in order to improve oral bioavailability, formulation, water solubility, and simultaneous byproduct formation is suggested", it teaches that these advantages can be expected by combining the sulbactam not only with the penicillin under discussion, but with other β-lactams as well. Therefore, for any other mixture of sulbactam

with another drug which one would be motivated to use in the first place --- motivated by the fact that the two form a synergistic combination --- one can get that improved "oral bioavailability" and all the rest by converting the pair into a carboxyl-terminated double-ester prodrugs, i.e. applicants compound.

Next, applicants state, "In Baltzer and English, the specific sort of β-lactam antibiotic, Cephalosporin, has not been mentioned at all. In particular, no preparation of a series of β-lactam resistant cephalosporin ester compound and salts thereof, as well as their use for preparation of the antibiotics, has been disclosed or suggested. This same situation applies to Xiong (2004)." This treats the rejection as being an anticipation over Baltzer or English or Xiong. It is not. It is an obviousness rejection over the combination of references.

Next, in point 13, applicants provide a long quotation that "Lord Wilberforce judged", from a document which applicants have not provided, and in point 14 applicants draw inferences from this. Applicants wording of "...the Case DuPont'd (Witsiepe) Application .... " makes it appear that this is a decision from some foreign tribunal, possibly New Zealand. Prosecution of US patent applications is done entirely on the basis of US patent law. No weight can be given to this. Much the same is true for point 15, which appears to be some legal analysis by a European Patent Office Technical Board of Appeals.

Next, applicants state, "Please note the content of EPC Art. 56 is similar or almost identical with the meaning of 35 USC §103." First, none of the previous sections made any mention of EPC Art. 56, and even if these did, it is not relevant. The analysis is done under 35 USC §103, not something "similar" to it.

In paragraph 17, applicants argue that their compound have "indisputable novelty" and that their compounds are "sup[ported by the whole content of the Application." Agreed.

Next, applicants quote from three sentences, and state that the third sentence should have been worded "an expectation is already anticipated". It is unclear what that proposed replacement sentence is supposed to mean, but at any rate, the sentence as it appeared in the office action was correct and does express the examiner's position. Applicants conclude this point by saying " Applicants believe that an expectation or an anticipation, without selection of the more precisely prescribed substances, cannot take away the novelty as well as the non- obviousness of the presently pending claims." Again, novelty is not the issue. Beyond that, it is not entirely clear what applicants point here is. The specific substances at issue, viz, the sulbactam, the particular cephalosporin, and the specific feature of esterifying both of them to the same methylene group is specifically taught.

Next, applicants quote the examiner's description of the Xiong reference, and state, "Applicants respectfully submit that the Examiner made a conclusion based on a wrong concept as well. Table 2 merely show "Results of susceptibility testing for transformants", which, as stated by Xiong (2004) on page 266, under "4. Discussion", merely indicates "...the possibility of horizontal transfer of the resistance gene." The results do mention the "possibility of horizontal transfer of the resistance gene" but that is not the aspect of the reference which the examiner relies on. The examiner relies on Table 2. This shows that the ß-lactamase inhibitor Sulbactam (an irreversible inhibitor of ß-lactamase; it binds the enzyme thus preventing it from destroying the ß-lactam antibiotic by opening its lactam ring) has a strong synergistic effect on the effectiveness of assorted ß-lactam antibiotics, which of course is the sole reason that ß-lactamase inhibitors are used. For example, for cefuroxime alone, in the testing against SHV-12, the MIC was 64 mg/l. When it was

combined with the ß-lactamase inhibitor sulbactam, that number was reduced to 2 --- the synergistic combination was 32 times more effective that with the ß-lactam cefuroxime alone, showing that sulbactam has hugely potentiated the cefuroxime. In fact, the other two ß-lactamase inhibitors clavulanic acid and tazobactam also gave very strong synergism. In the testing with CTM-M-3, the effect was even more dramatic. For cefuroxime alone, the MIC was >128 mg/l, meaning that they could not get the inhibition even at the highest concentration tested. But in combination with sulbactam, they obtained a value of 4mg/l. It did this with Cephalothin, Cefpodoxime, Cefotaxime, Ceftazidime and Ceftriaxone as well. Therefore, when e.g. English says that one can get the listed advantages when sulbactam is combined with other drugs to form carboxyl-terminated double-ester prodrugs, it would be obvious and desirable to use the sulbactam-cefuroxime combination, because sulbactam is known to strongly potentiate the cefuroxime.

Applicants next point to their "improved antibacterial effect" pointing to Applicants' Experiment results on page 21 and pages 23-24. This is discussed below.

Applicants next state "...the Examiner has misunderstood the references. That is, the methods disclosed in English are not a same, and do not even pertain to the precisely prescribed substances as recited in Applicants' claim 16...." The examiner has not misunderstood the English reference; it is applicants who have misunderstood the rejection. Yes, the substances in claim 16 are not the "same" as English, but English is not an anticipatory reference. It is used in combination with Xiong (2004).

Applicants point to their "improved antibacterial effect" pointing to Applicants' Experiment results on page 21 and pages 23-24, applicants are unpersuaded by the analysis given above in point E. It is not entirely clear what point applicants make at the

beginning of the discussion, but the examiner agrees that β-lactams vary in their specificity, and that there are both gram positive and gram negative bacteria. However, applicants have not dealt with the essential thrust of the examiner's argument. There are always variations from one strain to another, this is expected, not unexpected. However, taken as a whole, the claimed ester was better than the combination in only 6 cases, the same in 14, and worse in 12. Overall, the esters performed more poorly. Looking at the results as a whole, at all the results, is what is required. Determination of unexpected effects entails looking at both differences and similarities. If there are "too many similarities and too few differences", then unexpected effects cannot be considered demonstrated, ***Sterling Drug Inc. v. Brenner***, 150 USPQ 584. Similarly, ***In re GRAF***, 145 USPQ 197 states, "the conclusion required under section 103 must be grounded on a weighing of all the facts." (emphasis added). Cf. also ***In re DE MONTMOLLIN AND RIAT***, 145 USPQ 416; ***In re Nolan***, 193 USPQ 641. Further, as the examiner has pointed out in point c., even the improvements are expected, because both the primary references tell one of ordinary skill in the art to expects an improvement from the prodrug approach. Thus, it is not enough even for those few cases where there was an improvement, so say that it is "improved"; applicants must establish why this improvement is unexpected (see e.g. ***In re Geisler***, 43 USPQ2nd 1362), in light of the art.

Applicants next cite another legal analysis by a European Patent Office Technical Board of Appeals in another unrelated case, which has o bearing on this situation for reasons set forth above.

Specification

The new specification is entered. For the record, the Chinese characters which needed to be removed were indeed Chinese characters which originally appeared at the top of page 9, in the last two lines of the second example 1 table and elsewhere (end of example 5). These have now been replaced with the word "or" which resolves the problem. Applicants have also removed the Greek letter epsilon, which is not a problem.

The Method 2 scheme has been amended but needs another repair. The final product has the oxygen at the lower right in the wrong place.

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, THIS ACTION IS MADE FINAL even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark L. Berch whose telephone number is 571-272-0663. The examiner can normally be reached on M-F 7:15 - 3:45.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on (571)272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Mark L. Berch
Primary Examiner
Art Unit 1624

9/8/2009